II. Remarks

Reconsideration and allowance of the subject application are respectfully requested.

Applicant has amended Claim 1 to clarify that the subject matter covered thereby relates to a method of inhibiting a neurotrophin-mediated activity in a mammal comprising the step of administering to the mammal an effective amount of a pharmaceutical composition comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. A minor amendment has been effected to Claims 2-4, so that these claims are now directed to a method. Claim 5 has been amended to clarify that the subject matter covered thereby relates to a method of inhibiting a neurotrophin-mediated activity in a mammal comprising the step of administering to the mammal an effective amount of a pharmaceutical composition comprising a compound selected from a prescribed list of compounds or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. A minor amendment has been effected to Claims 6-7 such that these claims are now directed to a method. Claim 9 has been cancelled without prejudice or disclaimer. Claim 10 has been amended to be in a form consistent with the amendment to Claim 1. Claim 11 has been cancelled without prejudice or disclaimer. Claim 12 has been amended to depend from Claim 1. Claim 13 has been amended to have a similar form to amended Claim 5. Claim 20 has been amended to clarify that the subject matter covered thereby relates to a method of inhibiting a neurotrophin-mediated activity in a mammal comprising the step of administering to the mammal an effective amount of a pharmaceutical composition comprising a specific compound or its pharmaceutically acceptable salt, and a pharmaceutically

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acceptable carrier. Claim 21 has been cancelled without prejudice or without disclaimer. Claim 22 has been amended in a manner similar to Claim 10. Claims 23 and 25-34 have been cancelled without prejudice or disclaimer. Claims 35-38 are new and refer to specific undesirable types of neurotrophin-mediated activity referred to on page 5, lines 26 to page 6, line 1 of the present application. Finally, Claims 1-3, 5 and 6 have been amended to correct the spelling of the term "benzimidazol-2-yl".

It is believed that no new subject matter has been added by the amendments submitted herewith.

Accordingly, Claims 1-7, 10, 12-13, 20, 22, 24 and 35-38, currently stand in the present application. Claims 1, 5, 13 and 20 are independent.

In Paragraph 2 of the outstanding Official Action, the Examiner withdraws Claims 14-19 from further consideration as purportedly being drawn to a non-elected invention.

In Paragraph 3 of the outstanding Official Action, the Examiner also withdraws Claims 22-34 on the basis that these claims are directed to treating different types of pain which would be grouped with Group II (Claim 14), drawn to the method of treating pain. In response, Applicant wishes to point out that Claims 22 and 24 have been amended such that they are directed to the invention originally elected for prosecution in the present application. Further, for the record, Applicant reserves the right to file one or more divisional or related applications: (i) for the subject matter of the claims withdrawn by the Examiner, or (ii) claiming any other subject matter supported

by the present application. Cancellation of any claims in the present application should not be confused with acquiescence to the propriety of any statutory or other objection previously raised by the Examiner.

In Paragraphs 4 and 14 of the Official Action, the Examiner rejects Claims 1-4 and 9-12 under the judicially created doctrine of obviousness-type double patenting as purportedly being unpatentable over Claims 1-18 of United States patent 6,492,380 in view of Bundgaard. This rejection is traversed. Reconsideration is requested.

To meet the initial threshold test to raise an obviousness-type double patenting rejection between an application and a patent directed to purportedly non-patentably distinct inventions, there must be at least one common inventor named on the application and the patent or there must be common ownership between the application and the patent. In the present case, there is currently no named inventor who is common to both the present application and United States patent 6,492,380. Further, there is no common ownership between the present application and United States patent 6,492,380. The Examiner is directed to Chart II-B in Chapter 8 of the MPEP which states that, in a situation where there is no common assignee or inventor in the application and the patent, the appropriate rejection is one under 35 U.S.C. §102(a)/§103(a). In the current circumstances, the present application has an earlier priority date than that of United States patent 6,492,380 and thus, the latter is not citable under 35 U.S.C. §102(a)/§103(a).

The Examiner is requested to reconsider and withdraw the obviousness-type double

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patenting rejection.

In Paragraph 6 of the Official Action, the Examiner rejects Claims 1-4 and 9-12 under 35 U.S.C. §112 (first paragraph) as purportedly failing to comply with the written description requirement. The Examiner particularly objects to proviso (ii) in Claim 1. However, the Examiner misstates this proviso as "the compound wherein when R3 is nitro, R1 is benzyl". The Examiner asserts that this is not described in the specification. The Examiner further asserts that R1 as benzyl is not described in any of the Examples. This rejection is traversed. Reconsideration is requested in light of the following remarks.

Preliminarily, Applicant wishes to state that the Examiner has misstated proviso (ii). Specifically, this proviso reads "when R^3 is NO_2, R^1 is not benzyl". Applicant has previously provided the Examiner with a concordance of chemical structures and chemical names for the compounds specifically mentioned in the present application on page 8, lines 3 to page 9, line 23 – see the Appendix to Applicant's Amendment filed on November 17, 2003. This Appendix clearly illustrates that, in 16 of the 39 compounds mentioned, one of the R^2 or R^3 is nitro and, in each of the 16 compounds, R^1 is not benzyl. Applicant submits this is ample support for proviso (ii) in Claim 1.

The Examiner is requested to reconsider and withdraw the rejection of Claims 1-4 and 9-12 under 35 U.S.C. §112 (first paragraph).

In Paragraph 8 of the Official Action, the Examiner rejects Claims 1-7, 9-12, 14, 20 and 21 under 35 U.S.C. §102(f) on the basis that Applicant purportedly did not invent the claimed

subject matter. To substantiate the rejection, the Examiner cites Owolabi et al. [Owolabi]. This rejection is traversed. Reconsideration is requested.

Owolabi is a journal article that was received for publication on October 22, 1998, accepted for publication on February 17, 1999 and actually published thereafter. All of these dates are of course after the earliest priority date (i.e., October 21, 1996) of the present application. Further, all of these dates fall after the publication date of the International patent application (i.e., WO 98/17278, published on April 30, 1998) corresponding to the present application. Further, Owolabi is co-authored by Ashok Tehim, one of the named inventors in the present application. In the circumstances, Applicant submits that the Examiner has failed to make a prima facie showing with any evidence that another made the invention and that Applicant derived the invention from the true inventor(s). Absent such evidence, the Examiner must presume the named inventors in the present application are the proper inventors – see Chapter 706.02(g) of the MPEP.

The Examiner is requested to reconsider and withdraw the rejection of Claims 1-7, 9-12, 14, 20 and 21 under 35 U.S.C. §102(f).

In Paragraph 10 of the Official Action, the Examiner rejects Claims 1-7, 9, 20 and 21 under 35 U.S.C. §103(a) as being purportedly unpatentable over reference AZ2 in view of Gray et al. and/or Kubinyi. The Examiner asserts:

> "For a composition claim, the intended use fails to set a demarcation from the prior art composition comprising the same compound."

Applicant traverses the rejection. Reconsideration is requested in light of the following remarks.

As the Examiner will note, all current claims in the present application relate to a method of inhibiting a neurotrophin-mediated activity in a mammal comprising administering to the mammal a prescribed composition. None of reference AZ2, Gray et al. and/or Kubinyi, taken alone or in combination, teach or suggest a composition for or a method of inhibiting a neurotrophin-mediated activity in a mammal. The "demarcation" referred to by the Examiner is clearly in the current Claims and Applicant submits that the rejection in Paragraph 10 of the Official Action is moot.

The Examiner is requested to reconsider and withdraw the rejection of Claims 1-7, 9, 20 and 21 under 35 U.S.C. §103(a).

In Paragraph 11 of the outstanding Official Action, the Examiner rejects Claims 5, 6 and 13 under 35 U.S.C. §103(a) as being purportedly unpatentable over Brana III [Brana] in view of Bundgaard. This rejection is traversed. Reconsideration is requested in light of the following remarks.

Initially, as acknowledged by the Examiner, Brana teaches certain bisnaphthalimides and states that these compounds "have better action or a better action spectrum as tumor-inhibiting substances and possess antileukemic activity" – see column 1 lines 41-43. Brana does not teach or suggest any composition for or method of inhibiting a neurotrophin-mediated activity in a mammal

as set out in the current claims. Accordingly, it is believed that the rejection of Claims 5, 6 and 13 in Paragraph 11 of the outstanding Official Action is moot.

Notwithstanding this, Applicant is nonplussed that the Examiner can take the position that one would be motivated to modify the compounds of Brana "to arrive at the instant invention with a reasonable expectation of obtaining and [*sic*] additional anti-rumor composition". Specifically, to substantiate a later rejection under 35 U.S.C. §112 (first paragraph), the Examiner makes the following statements:

> "The high degree of unpredictability is well-recognized in the pharmaceutical art. A slight modification of the compound would drastically change its biological activity (Jaen, columns 14-15, Table I). Structural requirements for binding to the receptor are absolute (LeSaulteur, abstract; page 6567 Table II, Table III)." (emphasis added)

The Examiner cannot have it both ways. If small structural changes to known chemical compounds lead to drastic changes in the biological activity of the new compounds and this leads to a "high degree of unpredictability" in the pharmaceutical art, a rejection such as the one set out in Paragraph 11 of the outstanding Official Action cannot be sustained.

The Examiner is requested to reconsider and withdraw the rejection of Claims 5, 6 and 13 under 35 U.S.C. §103(a).

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In Paragraph 12 of the outstanding Official Action, the Examiner rejects Claims 1-4 and 9-12 under 35 U.S.C §103(a) as being purportedly unpatentable over Sestanj I [Sestanj] in view of Malizia and Bundgaard. This rejection is traversed. Reconsideration is requested in light of the following remarks.

Sestanj teaches certain benzoisoquinoline acetic acid derivatives useful for the production of pharmaceutical compositions that can be administered to a diabetic mammal whereby diabetic complications are prevented or relieved – see column 1, line 53 to column 2, line 2.

Malizia refers to Sestanj on page 2, lines 12-16 and teaches that compositions containing a propionic acid homolog of the compounds taught by Sestanj are "surprisingly more active and endowed with more advantageous pharmaco-therapeutics characteristics" – see page 2, lines 16-19.

The Examiner relies on Bundgaard for the purported teaching of an ester-based prodrug.

Of particular note, and contrary to the Examiner's contention, neither Sestanj nor Malizia, taken alone or in combination, teach a compound encompassed by any claim in the present application. In Paragraph 12, of the outstanding Official Action, the Examiner appears to imply that the propionic acid homolog of the compound taught by Sestanj is encompassed by the compound of Formula I in Claim 1 of the present application. This is incorrect. The attention of the Examiner is directed particularly to the following language of Claim 1 for the definition of R^1: "C_2-C_4 alkyl-

$(R^5)(R^6)$ wherein one of R^5 and R^6 is selected from H and loweralkyl and the other is selected from carboxy-loweralkyl and loweralkoxycarbonyl". This language does not include propylcarboxy within the scope of R^1. The teachings of Bundgaard do not alter the above analysis.

Notwithstanding this, as stated above, the current claims in the present application relate to a method of inhibiting a neurotrophin-mediated activity in a mammal. Neither Sestanj nor Malizia, taken alone or in combination, teach or suggest any composition for or method of a inhibiting a neurotrophin-mediated activity in a mammal as set out in the current claims.

Still further, Applicant incorporates herein the comments above made in response to Paragraph 11 of the outstanding Official Action relating to the inconsistent approach adopted by the Examiner in justifying the obviousness rejection based on purportedly minor changes in chemical compounds while at the same time making the broad statements of unpredictability set out in Paragraph 17 of the outstanding Official Action.

Accordingly, the Examiner is requested to reconsider and withdraw the rejection of Claims 1-4 and 9-12 under 35 U.S.C §103(a) as being purportedly unpatentable over Sestanj in view of Malizia and Bundgaard.

The Examiner's objection in Paragraph 13 of the outstanding Official Action is moot in light of cancellation of Claim 9 without prejudice or disclaimer.

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In Paragraph 15 of the outstanding Official Action, the Examiner rejects Claims 1-7, 9-13 and 21 under 35 U.S.C. §112 (second paragraph) as being purportedly indefinite. This rejection is traversed. Reconsideration is requested in light of the following remarks.

The Examiner rejected Claims 1-7 and 9-12 for inclusion of the term "mediated". Applicant refers the Examiner to page 5, lines 26-27 wherein there is provide a clear definition of the term "neurotrophin-mediated activity". Applicant submits that the term "mediated" contained in "neurotrophin-mediated activity" would be clear and definite to a person of ordinary skill in the art having in hand the specification of the present application. Specific examples of neurotrophin-mediated activities are disclosed at page 5, line 27 to page 6, line 1 of the present application. How to test for inhibition of certain neurotrophin-mediated activities is disclosed at page 6, lines 3-8 of the present application.

The Examiner rejected Claim 13 on the basis that "the substituents on the ester or amide" were not defined. Claim 13 refers to an *in vivo* hydrolyzable ester or amide – there is no reference to substituent. Further, as acknowledged by the Examiner in Paragraph 11 of the outstanding Official Action, an ester or amide of an active ingredient is an "art-recognized prodrug". Accordingly, it is submitted that a person of ordinary skill in the art would have no difficulty understanding the meaning of the term "hydrolyzable ester or amide" as used in Claim 13.

The Examiner is requested to reconsider and withdraw the rejection of Claims 1-7, 9-13 and 21 under 35 U.S.C. §112 (second paragraph).

In Paragraph 16 of the outstanding Official Action, the Examiner rejects Claims 1-7, 9-12 and 21 under 35 U.S.C. §112 (first paragraph) as purportedly failing to comply with the written description requirement. Here, the Examiner asserts:

> "The 'neurotropin-mediated activity' [*sic*] encompasses conflicting conditions or diseases and reaches out to conditions or diseases not yet discovered."

The Examiner's statement concerning "conflicting conditions or diseases" is not understood. On page 1, line 16 to page 2, line 29 present application , there is a clear and concise discussion of the function of neurotrophins and their role in certain diseases or conditions. Various of these diseases or conditions are mentioned at page 2, lines 19-24 of the present application. Even though there are different conditions or diseases, it is not seen how these different conditions or diseases are "conflicting".

The Examiner's remark that neurotrophin-mediated activity "reaches out to conditions or diseases not yet discovered" is, in Applicant's submission, irrelevant. The subject matter of the claims in the present application is directed to the use of prescribed compounds to inhibit a neurotrophin-mediated activity in a mammal. Applicant submits that it is not relevant whether all conditions or diseases (known or unknown) that are underpinned by neurotrophin-mediated activity are mentioned in the specification for the purposes of determining compliance with 35 U.S.C. §112 (first paragraph). Applicant clearly possesses the claimed invention, namely the method of inhibiting

a neurotrophin-mediated activity in a mammal comprising administration of prescribed compounds to a mammal.

The Examiner further asserts:

> "A full description of 'the neurotropin-mediated activity' [*sic*] is not described in the specification."

In response, Applicant wishes to advise the Examiner that the term "neurotrophin-mediated activity" is defined and exemplified in the present application on page 5, line 26 to page 6, line 8.

In the circumstances, the Examiner is requested to reconsider and withdraw the rejection of Claims 1-7, 9-12 under 35 U.S.C. §112 (first paragraph).

In Paragraph 17 of the outstanding Official Action, the Examiner rejects Claims 1-7, 9-12 and 21 under 35 U.S.C. §112 (first paragraph) on the basis that the specification purportedly does not provide enablement for treatment of any "neurotropin-mediated activity" [*sic*] beyond the treatment of pain. This rejection is traversed. Reconsideration is requested in light of the following remarks.

With regard to Paragraph 17a of the outstanding Official Action, Applicant disagrees with the Examiner's contention that the instant invention "is drawn to a naphthaimide [*sic*] compound for inhibiting neurotropin-mediated [*sic*] activity". Rather, Applicant submits that the

present invention, as defined by the claims currently on file, relates to the use of prescribed naphthalimide compounds for inhibiting a neurotrophin-mediated activity in a mammal.

With regard to Paragraph 17b of the outstanding Official Action, the Examiner states that the nexus between inhibition of neurotrophin and the treatment of all recited diseases or conditions has not been fully established. In response, Applicant incorporates here the remarks made above in response to Paragraph 16 of the outstanding Official Action.

With regard to Paragraph 17c of the outstanding Official Action, Applicant disagrees with the contention that "a correlation between the inhibition of NGF binding and the biological response has not been fully established". To the contrary, the present application provides ample experimental evidence that there is indeed a correlation between inhibition of NGF binding and the biological response as described on page 5, line 27 to page 6, line 8, and as mentioned in the Examples. Thus, Applicant submits that there is sufficient basis to extrapolate the so-called binding data to various *in vivo* situations involving different target tissues.

With reference to Paragraph 17d of the outstanding Official Action, Applicant is nonplussed that the Examiner can take the position that an example of an *in vivo* hydrolysable ester or amide of the compounds referred to in the claims has not been shown nor has the process to produce same been shown. Specifically, in Paragraphs 11 and 12 of the outstanding Official Action, the Examiner repeatedly relies on Bungaard for the teaching that "ester or amide is [an] art-

recognized prodrug". Adopting the Examiner's earlier position in these Paragraphs of the Official Action, the assertion made in Paragraph 17d is moot.

With regard to Paragraph 17e of the outstanding Official Action, the Examiner appears to be taking the position that extrapolation from the Examples of the present application (Compound A) to other compounds covered by the claims purportedly is not commensurate with the scope of the objective enablement. To the contrary, Applicant submits the examples provided in the present application, together with the remainder of the specification, provide ample support for extrapolating the specific results in the working Examples to other compounds covered by the present claims. With regard to the so-called "conflicting conditions or diseases", this issue has been dealt with above in responding to Paragraph 16 of the outstanding Official Action.

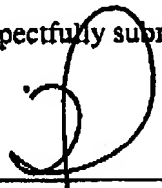
With reference to Paragraph 17f of the outstanding Official Action, this is simply a summary of the various points referred to in Paragraphs 17a-17e. Applicant has rebutted each of the Examiner's assertions in Paragraphs 17a-17e. Accordingly, Applicant submits that the present application provides sufficient teaching and guidance to one ordinary skill in the art to use the compounds covered by the claims of the present application for inhibiting a neurotrophin-mediated activity in a mammal.

The Examiner is requested to reconsider and withdraw the rejection of Claims 1-7, 9-12 and 21 under 35 U.S.C. §112 (first paragraph).

It is believed that the above remarks and amendments submitted herein have placed

this present application in condition for allowance, and a Notice thereof is requested. If the Examiner has further concerns, she is encouraged to contact Applicant's undersigned agent at 416-862-5775. All correspondence should continue to be directed to listed address shown below.

Respectfully submitted,



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